Claims:

1. An herpes simplex virus wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous nitroreductase (NTR).

2. An herpes simplex virus as claimed in claim 1 wherein said NTR is E.coli NTR.

3. An herpes simplex virus as claimed in claim 2 wherein said nucleic acid comprises SEQ ID No. 2 or nucleic acid encoding the polypeptide of SEQ ID No. 1.

4. An herpes simplex virus as claimed in claim 1 wherein said nucleic acid has at least 60% sequence identity to SEQ ID No. 2 or to a nucleic acid encoding the poplypeptide of SEQ ID No. 1.

5. An herpes simplex virus as claimed in claim 4 wherein said degree of sequence identity is at least 70%.

6. An herpes simplex virus as claimed in claim 1 wherein said nucleic acid hybridises to the nucleic acid of SEQ ID No. 2, to its complement or to a nucleic acid encoding the polypeptide of SEQ ID No. 1 under high stringency conditions.

7. An herpes simplex virus according to any one of claims 1 to 6 wherein said herpes simplex virus genome further comprises a regulatory nucleotide sequence operably linked to said nucleic acid encoding NTR,

wherein said regulatory nucleotide sequence has a role in controlling transcription of said NTR.

8. An herpes simplex virus as claimed in any one of claims 1 to 7 wherein said nucleic acid is located in at least one RL1 locus of the herpes simplex virus genome.

9. An herpes simplex virus as claimed in any one of claims 1 to 8 wherein said nucleic acid is located in, or overlaps, at least one of the ICP34.5 protein coding sequences of the herpes simplex virus genome.

10. An herpes simplex virus as claimed in any one of claims 1 to 9 wherein the herpes simplex virus is a mutant of one of HSV-1 strains 17 or F or HSV-2 strain HG52.

11. An herpes simplex virus as claimed in any one of claims 1 to 9 wherein the herpes simplex virus is a mutant of HSV-1 strain 17 mutant 1716.

12. An herpes simplex virus as claimed in any one of claims 1 to 11 which is a gene specific null mutant.

13. An herpes simplex virus as claimed in any one of claims 1 to 12 which is an ICP34.5 null mutant.

14. An herpes simplex virus as claimed in any one of claims 1 to 11 which lacks at least one expressible ICP34.5 gene.

15. An herpes simplex virus as claimed in any one of claims 1 to 10 which lacks only one expressible ICP34.5 gene.

16. An herpes simplex virus as claimed in any one of claims 1 to 15 which is non-neurovirulent.

17. An herpes simplex virus as claimed in any one of claims 1 to 16 wherein said nucleic acid encoding the heterologous nitroreductase (NTR) forms part of a nucleic acid cassette integrated in the genome of said herpes simplex virus, said cassette encoding:

(a) said nucleic acid encoding NTR; and nucleic acid encoding

(b) a ribosome binding site; and

(c) a marker,

wherein the nucleic acid encoding NTR is arranged upstream (5') of the ribosome binding site and the ribosome binding site is arranged upstream (5') of the marker.

18. An herpes simplex virus according to claim 17 wherein a regulatory nucleotide sequence is located upstream (5') of the nucleic acid encoding NTR, wherein the regulatory nucleotide sequence has a role in regulating transcription of said nucleic acid encoding NTR.

19. An herpes simplex virus according to claim 17 or 18 wherein the cassette disrupts a protein coding sequence resulting in inactivation of the respective gene product.

20. An herpes simplex virus as claimed in any one of claims 17 to 19 wherein a transcription product of the cassette is a bi- or poly- cistronic transcript comprising a first cistron encoding the NTR and a second cistron encoding the marker wherein the ribosome binding site is located between said first and second cistrons.

21. An herpes simplex virus as claimed in any one of claims 17 to 20 wherein the ribosome binding site comprises an internal ribosome entry site (IRES).

22. An herpes simplex virus as claimed in any one of claims 17 to 21 wherein the marker is a defined nucleotide sequence encoding a polypeptide.

23. An herpes simplex virus as claimed in claim 22 wherein the marker comprises the Green Fluorescent Protein (GFP) protein coding sequence or the enhanced Green Fluorescent Protein (EGFP) protein coding sequence.

24. An herpes simplex virus according to any one of claims 17 to 21 wherein the marker comprises a defined nucleotide sequence detectable by hybridisation under high stringency conditions with a corresponding labelled nucleic acid probe.

25. An herpes simplex virus as claimed in any one of claims 17 to 24 wherein the cassette further comprises nucleic acid encoding a polyadenylation sequence located downstream (3′) of the nucleic acid encoding the marker.

26. An herpes simplex virus as claimed in claim 25 wherein the polyadenylation sequence comprises the Simian Virus 40 (SV40) polyadenylation sequence.

27. An herpes simplex virus as claimed in any one of claims 1 to 26 for use in a method of medical treatment.

28. An herpes simplex virus as claimed in any one of claims 1 to 26 for use in the treatment of cancer.

29. An herpes simplex virus as claimed in any one of claims 1 to 26 for use in the oncolytic treatment of a tumour.

30. Use of an herpes simplex virus as claimed in any one of claims 1 to 26 in the manufacture of a medicament for the treatment of cancer.

31. A method of lysing or killing tumour cells in vitro or in vivo comprising the step of administering to a patient in need of treatment an herpes simplex virus as claimed in any one of claims 1 to 26.

32. A medicament, pharmaceutical composition or vaccine comprising an herpes simplex virus as claimed in any one of claims 1 to 26.

33. A medicament, pharmaceutical composition or vaccine as claimed in claim 32 further comprising a pharmaceutically acceptable carrier, adjuvant or diluent.

34. An herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase (NTR) in at least one of the long repeat regions (R_L).

35. An herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase (NTR) and wherein the herpes simplex virus is non-neurovirulent.

36. A composition comprising a herpes simplex virus according to claim 34 or claim 35 and an NTR prodrug.

37. A composition as claimed in claim 36 wherein said NTR prodrug is CB1954.

38. An herpes simplex virus for use in the treatment of a tumour, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long repeat regions (R_L).

39. An herpes simplex virus for use in the treatment of a tumour, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase and wherein the herpes simplex virus is non-neurovirulent.

40. An herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long

repeat regions (R_L), for use, in combination with an NTR prodrug, in the treatment of a tumour.

41. An herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase and wherein the herpes simplex virus is non-neurovirulent, for use, in combination with an NTR prodrug, in the treatment of a tumour.

42. A kit of parts comprising a first container having a quantity of herpes simplex virus according to any one of claims 1 to 26, 34 or 35 and a second container having a quantity of an NTR prodrug.

43. Use of an herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long repeat regions (R_L), in the manufacture of a medicament for the treatment of a tumour.

44. Use of an herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase and wherein the herpes simplex virus is non-neurovirulent, in the manufacture of a medicament for the treatment of a tumour.

45. Use in the manufacture of a medicament for the treatment of a tumour of a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at

least one of the long repeat regions (R_L), and an NTR prodrug.

46. Use in the manufacture of a medicament for the treatment of a tumour of a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase and wherein the herpes simplex virus is non-neurovirulent, and an NTR prodrug.

47. Use of a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long repeat regions (R_L) in the manufacture of a first medicament for administering sequentially or simultaneously with a second medicament comprising an NTR prodrug in the treatment of a tumour.

48. Use of an NTR prodrug in the manufacture of a first medicament for administering sequentially or simultaneously with a second medicament comprising a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long repeat regions (R_L), in the treatment of a tumour.

49. Use of an NTR prodrug in the manufacture of a first medicament for administering sequentially or simultaneously with a second medicament comprising a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase and wherein the herpes

simplex virus is non-neurovirulent, in the treatment of a tumour.

50. Use of a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase and wherein the herpes simplex virus is non-neurovirulent, in the manufacture of a first medicament for administering sequentially or simultaneously with a second medicament comprising an NTR prodrug, in the treatment of a tumour.

51. A method for the treatment of a tumour comprising the steps of:

(i) administering to a patient in need of treatment a therapeutically effective amount of a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding a nitroreductase in at least one of the long repeat regions (R_L); and

(ii) administering to said patient a therapeutically effective amount of an NTR prodrug.

52. A method for the treatment of a tumour comprising the steps of:

(i) administering to a patient in need of treatment a therapeutically effective amount of a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding a nitroreductase and wherein the herpes simplex virus is non-neurovirulent; and

(ii) administering to said patient a therapeutically effective amount of an NTR prodrug.

53. The method of claim 51 or 52 wherein said herpes simplex virus is capable of killing tumour cells.

54. The virus, kit, use or method as claimed in any one of claims 38 to 53 wherein said NTR prodrug is CB1954.

55. A method of expressing in vitro or in vivo a nitroreductase, said method comprising the step of infecting at least one cell or tissue of interest with a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long repeat regions (R_L), said nitroreductase operably linked to a transcription regulatory sequence.

56. A method of expressing in vitro or in vivo a nitroreductase, said method comprising the step of infecting at least one cell or tissue of interest with a non-neurovirulent herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase, said nitroreductase operably linked to a transcription regulatory sequence.

57. HSV1716/CMV-NTR/GFP (ECACC accession number 03110501).